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         Randomized Trial in the Philippines

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13. ABSTRACT (Maximum 200 Words)
Most breast cancer cases in the Philippines present at advanced stages and have a rapid unfavorable outcome. BCE undertaken by health workers appears to be an attractive compromise with a good cost-effectiveness ratio suitable for a country with limited resources. However, the sensitivity of the screening program in the real context is very low. Moreover, despite high compliance with the examination, this intervention failed to improve compliance with clinical investigation.

<u>Completed activities.</u>
Data analysis and reporting of the core results.

<u>On-going</u>
Several additional aspects related to the risk, management and care of breast cancer are being analyzed.

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Table of Contents

INTRODUCTION

In year 2000 breast cancer accounted for over 1 million new cases per year worldwide; it is the most common cancer in women, and incidence rates are still rising, particularly in low-risk countries[1]. It seems that these trends are likely to continue, since the current pattern of later childbearing, decreasing fertility, increasing height and weight and 'westernization' of diets will all be associated with increased risk.

At present, our knowledge of environmental risk factors does not permit formulation of any practical primary prevention programmes. Significant improvements in the prognosis of early breast cancer have been achieved in the 80s and 90s[2,3]. The introduction of adjuvant therapy with Tamoxifen is the most recent innovation that had a significant impact on the survival of cases at all ages and is believed to be a major cause of the initial reduction of mortality observed in some high-risk countries[4, 5, 6, 7]. For treatment to be highly effective however, it is essential that the disease is detected at an early clinical stage.

The potential of optimal treatment is maximum when combined with screening programmes which lead to the detection of sub-clinical tumours, less malignant than those which surface clinically. An extensive and comprehensive review of the efficacy of different screening modalities for the breast has been published recently[8]. It concluded that there is sufficient evidence that mammography can reduce breast cancer mortality by 25% in women 50-69 years of age. It is also recognized that the performance of population screening programmes by mammography may achieve that impact on mortality only by maintaining high participation rates, high sensitivity of the test, accurate diagnostic investigation of screen-positive women, and timely treatment of detected cases. Mammography is an expensive technology that requires highly trained radiologists and radiographers. The cost per life-year saved, having to meet all the conditions described above, is therefore relatively high[9,10,11] and clearly an inappropriate use of health care resources for many low-income countries[12].

Other screening strategies that have been proposed are clinical examination of the breasts (CBE), and breast self-examination (BSE). The efficacy of BSE has been evaluated in one large scale randomised trial among 266,000 textile workers in Shanghai, China[13]. Biases such as low compliance with the intervention, failure of proper randomisation or low proficiency in performing BSE could be confidently excluded[14]. No significant reduction of breast cancer mortality in the intervention group was detected after 10 years of follow-up and the distributions of stage at diagnosis in screen and control groups were very similar. However, the small size of the lesions diagnosed in the control subjects in this trial (47 % ≤2 cm diameter, 48% node negative) suggests a high level of health-awareness in this special subset of the Shanghai population, and may give little scope for improvement in outcome through early detection by BSE.

At present CBE has never been used as the sole modality of screening in a randomised controlled trial, so that its efficacy is not known. In non-randomised screening settings, the clinical stage of cases detected by CBE is less advanced than those found in usual clinical practice[15,8]. In screening programmes employing both mammography and PE, cancer detection rates by the two methods suggest that CBE has about 2/3 to 3/4 of the efficiency of mammography in women aged 50 or more[8]. CBE alone may even be more effective in younger women, among whom up to 25% of cancers are missed by mammography; in addition, there is evidence that CBE improves the performance of mammography. The working group that reviewed the results of the Breast Cancer Detection Demonstration Project, the first large non-experimental evaluation of mammography, stated that high priority should be given to the evaluation of CBE as a single screening modality[16]. The second Canadian Breast Cancer Screening Study (CNBSS II), in which women aged 50-59 were screened annually by CBE only or by CBE plus mammography, found no significant difference in mortality from breast cancer in the two groups after 13 years follow-up[17]. This has been cited as evidence that CBE is as effective, in practice, as mammography.

The purpose of the present work was to establish 1) whether a program of mass screening by PE performed by trained paramedical personnel could be set up in a developing country as part of the routine activity of first level health services, and 2) whether and to what extent such a program could reduce mortality from breast cancer. The location is Metro Manila and Rizal Province of the Philippines. This population has a relatively high incidence of breast cancer, considerably above that of other Asian populations, and comparable to that in southern Europe.

BODY

Study design. The study was designed as a randomised controlled trial of the effect of five annual clinical examinations of the breasts (BCE) performed by trained nurses/midwives, in reducing mortality from breast cancer. Women aged 35-64 years, resident in the central, more urbanized municipalities of the National Capital Region of Manila were the target population. The area includes 12 municipalities (Figure 1) each having municipal health centres in the township area and barangay health stations in more rural areas. In 1990, the estimated size of the female population aged 35-64 was about 340,000. The units of randomisation were 202 health centres (HCs) within the selected municipalities.

Randomisation. In 1995 the Department of Health (DOH) provided information on the size and level of deprivation (2 levels and missing) of the population resident in each of the 202 HCs. These were grouped by deprivation index and size and, within each group, randomly assigned to intervention or control arm.

Identification of the eligible population. Nominative lists of women resident in the 12 municipalities and who were included in the electoral rolls were obtained from DOH. Women were identified by family and first name, date of birth, complete address (street and administrative area called barangay, which generally coincided with the area served by a health centre).

Interview of a sample of women resident in control areas. A random sample of names, stratified by age, was drawn from the file of the eligible population in the control HCs. Interviewers attempted to trace and interview women in the list according to the questionnaire used in the intervention cohort. The purpose of this sample survey was to estimate the actual proportion of the control cohort that was present in 1999, and to compare the characteristics of this cohort with those of the intervention group. This activity ceased when 1,000 interviews had been collected.

Intervention. During 1995 a coordinating centre was set up. Nurses and midwives were recruited and trained in the technique of CBE using the MAMACARE ™ [20] programme already developed and tested in the Philippines, that makes use of silicone models of the breast for training purposes[21]. Training was repeated for selected groups of examiners with detection rates markedly above or below the mean.

The first round of screening took place in 1995-1997 (30 months) and included 151,168 women.

Eligible women resident in the intervention HCs were contacted in two ways: at the HC among those women who were attending for a variety of reasons, and, for those who did not, by systematic home visits. The nature and purpose of the trial were explained, and women were asked to give a signed

assent to participation. They were interviewed, and CBE was carried out by the trained examiners. The interview addressed demographic variables and risk factors for breast cancer. Women were also instructed in the technique of breast self-examination (BSE) and provided with a leaflet in the local language explaining the purpose and methodology of BSE. Demographic characteristics of women who refused CBE were also recorded.

Women in whom abnormalities were detected were referred for diagnosis to special clinics that had been established in 3 major hospitals, and staffed by project personnel. The costs of transport to the clinic and of all medical procedures required to reach diagnosis were covered by the project. In addition, in final year of the intervention period, a mobile team, comprising a doctor and a nurse, and equipped to perform needle biopsies, carried out home visits for all positive women who had not reported to the referral centre, in order to obtain a final diagnosis.

Women in the control area received no active intervention, but were exposed to the general health education campaigns carried out by municipal authorities and voluntary bodies.

Follow-up. The aim of the follow-up of the intervention and control cohorts was to identify women who developed breast cancer and/or other cancers, those who died from other causes and those who migrated outside the study area.

The study populations were covered by two cancer registries, Manila-PCS and Rizal-DOH[19] (Fig.1). The case-finding procedures of both registries were enhanced, so that they took place in a more timely manner than previously. Additional staff was recruited and trained to trace cases and report data by means of new abstract forms which included detailed information on extent of disease, tumour size, spread and nodal involvement. All registered cases of breast cancer (resident in the study municipalities) were followed-up in 2001 to assess their vital status. Hospital records where first reviewed. Treating doctors and the cases' families were contacted for complement of information.

Project staff periodically visited the vital statistics offices of the 12 municipalities involved in the study to abstract information on all reported deaths, according to a standard notification form. The data were computerized and checked at the project office. The first follow-up phase (studying cancer incidence and mortality in the 2 years after the intervention) was completed in early 2002. The staff of the cancer registries who performed the follow-up was blind with respect to which cohort a case belonged.

Cases of breast cancer, and deaths from breast cancer, identified during the follow-up period were linked with the master file (interviews and CBE results) and lists of eligible populations (intervention and control areas) using a probabilistic record linkage software 'RECLINK'[1]. Records matched are distinguished in three groups depending on the value of the matching score: 1) definite match 2)

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[1] RECLINK is a record linkage software developed at unit of Descriptive Epidemiology, International Agency for Research on Cancer, Lyon. The software performs probabilistic linkage between records from different sources using selected personal identifiers (names, date of birth, sex, address, tribe).

possible match but requiring manual verification 3) non-match. Records in group 2) were verified using paper documents and a decision made.

Data analysis. Results are presented as absolute and relative frequencies, means and their standard deviations and 95% confidence limits (c.l.). Most comparisons are univariate or age-adjusted. Because of the huge numbers of subjects involved, statistical testing would not be informative and has been avoided when comparing cohorts. Confidence limits of proportions are based on the exact binomial distribution.

Results

Randomization. There were 101 HCs in each arm (intervention and control). The overall estimated number of people resident in the two arms was very similar, 1.82 million, as was the estimated proportion of deprived population, 29.2% in control areas and 28.8% in the intervention areas.

Nominative lists of the population. We compared the distributions of population by study arm and municipality based on the census data, nominative lists generated from electoral rolls and the questionnaires of interviewed women. Overall the three sources gave similar distributions with differences between any two in any one municipality that were less than 5%. The two exceptions were Pasig and Las Piñas in which census data estimate 6% more population (details not shown).

Intervention. The results of the intervention after completion of the single round of examinations, and the incidence of breast cancer in 2 years of follow-up are summarized in Table 1. The number of women interviewed and offered CBE was 151168; compliance with examination was 92% (138,392). Three thousand four hundred and eighty-three women (2.4% of those examined) were judged to have a lump at the first examination by the nurses, and were referred to the project clinics. Of these, 1293 (37.1%) received further investigation, and complete diagnostic follow-up was achieved for 1220 women (35% of those positive on screening).

1478 women (42.5%) actively refused further investigation, even with a home visit, and 785 (22.5%) were not traced, and were either reported by the neighbours or assumed to have moved away or died.

Among the 1220 women with complete follow-up 34 malignant cancers were detected; the presence of a lump was not confirmed in 563 (16.2%) and 623 (15.8%) were diagnosed as having benign breast disease.

Because of the poor compliance with follow-up of screen positive women, even with home visits, the active intervention was discontinued after completion of the first screening round in December 1997.

During the two years following the end of the intervention, 4 cases occurred among complying women initially diagnosed with benign disease; nine cases were identified among refusers and 10 in women not traced at follow-up.

Interview of women living in control areas. The nurses sought sequentially 1,624 women of the original list of names they were provided. Sixty-two percent of them (1,011 women) were located, of these 999 (99%) were interviewed. Of those not located 12 (0.7%) had died; 296 (18% of all) had moved away the remainder were incorrect addresses.

Comparison of characteristics of examined, refusers and control women.
Table 2 shows some socio-demographic characteristics of the three groups, women in intervention areas interviewed and examined, women interviewed who refused CBE and the sample of women resident in control areas. The three groups were very similar in age, 44.8±8.2 years, 44.7±8.4 and 44.0 ± 8.1 respectively, and were also of similar age at menarche, between 13.0 and 13.6 years. The three groups differed for other variables. Refusers were one year older than compliers at their first full-term pregnancy; controls were one year younger. Conversely, refusers were of higher socio-economical level than compliers as shown by the proportion of women who attended college (18% vs. 12%), had a significantly greater income (medians were Pesos 7,000/month vs 4,500), were more often nulliparous (17% vs. 10%) and less likely to have had 5 or more children (25% vs. 33%). Women interviewed in the control group were similar to refusers with respect to being of relatively high educational level (19% attended college). However, this sample declared a much lower income than the other two groups, a significant lower proportion was nulliparous (3%) and a lower proportion (21%) had had 5 or more children (21%). Thirteen percent of compliers stated that they were using oral contraceptives and 21% reported other contraceptive methods. The corresponding percentages were 9% and 13% among refusers and 6% and 9% among controls. Around 70% of the women in all groups had never had a cervical cytology test. Tobacco smoking is a rare habit in this population, 8% of compliers were regular smokers, 7% of refusers and 5% of control women. Eight percent of examined women regularly drank alcoholic beverages. The proportion was 11% among refusers but much higher among controls, 26%.

Detection rate by selected personal characteristics.
Among examined women the detection rate decreased constantly with age from 2.9% in women below 40 to 1.5% in women aged 60 or more (table 3). More women were detected positive among

those with less than three pregnancies (3.3% *vs.* 2.2%) and among those who attended cervical screening (3.3% *vs.* 2.1%). The detection rate was not consistently associated with the level of education and was higher in women with lower income. The detection rate ranged from 1.1% to 6.0% in the 12 municipalities. Rates above the average were recorded in the more affluent areas of Makati (4.0%), Mandaluyong (6.0%) and Malabon (3.9%).

Record linkage between Master Files (MFs) of women interviewed and lists of the eligible population.

The master files (MF) of the women interviewed were matched with the lists of the eligible populations, intervention and control cohorts, with the files of newly diagnosed cases and with death certificates. Only 19% of the women interviewed and examined in the intervention cohort were linked with records of women in the electoral rolls. The proportion of records matched varied significantly by municipality, 7% - 36%. In running the linkage procedure we adopted a conservative attitude maintaining only matches that scored at least 95%. The discrepancy reflects the high turn-over of the resident population. The electoral rolls released for the study had not been updated since the previous political elections.

Follow-up.

Information of persons dying and for whom cancer was recorded on the death certificate is part of the routine case-finding procedure for both cancer registries. Abstraction of information from death certificates at the vital statistics offices of the 12 municipalities was carried out at regular intervals as part of the enhanced case-finding referred to above. However, it became apparent that information from this source would be inadequate as a method of evaluating breast cancer mortality. Substantial omissions were evident, and the distribution of causes of death among records encoded in the first 6 months showed significant biases with cancer being over-represented. Here we report on the cumulative incidence (CI) of new cases that were included by the two cancer registries covering the municipalities where the project cohorts were recruited. Since we do not know the exact person-years of observation, rates were calculated as the number of new cases identified by 31 December 1999 in a cohort, divided by its size at recruitment. Date of recruitment of women in the control arm (that are known only through electoral rolls) was set to the mid-point of the recruitment period that is 1 December 1996.

Overall 518 breast cancer cases, incident in 1995-1999, were linked with records of women in the electoral rolls or in the intervention cohort, after exclusion of cases whose incidence date preceded date of recruitment. Figure 2 illustrates how they were partitioned by cohort, together with the cohort size. The CI of breast cancer was 11.6/10,000 women in the control arm, 9.7/10,000 in the intervention arm as identified by electoral rolls and 9.1/10,000 in the women invited for screening

(interviewed cohort). All of the 137 cases identified among interviewed cases had complied with CBE. Eighty of these had been judged negative on CBE (table 4) corresponding to a CI of 5.9 new cases per 10,000 women. 57 cases were detected among the 3,483 women who were screen-positive, 38 of which were diagnosed through the intervention itself (CI 2.8/10,000) although 4 were among women initially diagnosed with benign disease (table 4). Nineteen cases occurred among those women who did not complete the diagnostic process (CI 0.8/10,000). Table 4 also gives the cumulative incidence of BC by time since CBE. Thirty out of 38 screen-positive cases were diagnosed within 12 months of the first examination, only 4 were diagnosed later. All of the four malignant BC that occurred in women who were considered to have benign disease were diagnosed more than 12 months later. Of the 19 cases identified among refusers 11 occurred within a year and 8 later. The 80 cases diagnosed among screen-negative women were almost equally distributed between the two periods.

Table 5 shows the clinical extent of disease as recorded in the cancer registry database for the 34 cases who were correctly diagnosed as having cancer by the screening process, compared with the cases occurring in the women who were screened negative (80), who did not attend the diagnostic follow-up (19), or who were evaluated as having only benign disease when they did (4). None of the screen-detected cases had distant metastasis at presentation while 19.8% (95% c.i. 12%-30%) of the screen-negative group had metastatic disease. However, cases with localized disease were more common among screen-negatives, 20% *vs.* 11%. None of these differences were statistically significant.

Figure 3 shows the distribution and 95% c.i. by stage at presentation of the cases identified in the two arms (intervention and control) as defined by electoral rolls. The information was not available for 16% of the cases in both groups. Thirty-six percent of the cases were localized in the intervention group compared with 31% in controls, all at the expense of regional involvement the frequency of which was 49.7% (95% c.l. 42.1-57.3) and 53.8% (95% c.l. 46.3-61.2) respectively (not statistically significant). Fifteen percent of the cases presented with distant metastasis in both groups.

OCTOBER 2002 - SEPTEMBER 2003 ACHIEVEMENTS

During the period addressed by this annual report we completed the analysis of the screening intervention including the outcome of 2 years of follow-up. These results are presented in a manuscript currently under peer review with the Journal of the National Cancer Institute (JNCI manuscript reference No.03-0848).

In parallel, we continued the data management of information collected so far on aspects not directly related to the main objective of the study, reducing breast cancer mortality, but relevant and informative, that will be the object of further data analyses and publications.

WORK PLAN OCTOBER 2003-SEPTEMBER 2005

Our primary objective will be to complete the analysis of the data already collected and pursue reporting on scientific peer reviewed journals. The data available cover several subjects as follows:

A. Studies of factors that influence the risk of BC in the female Filipino population:

A.1   A case-control study nested in the intervention cohort, based on the 123 cases identified by record linkage, and 8 times as many controls. Controls were randomly extracted from the intervention cohort members to match cases on age ($\pm$ 3 yrs), date when examined ($\pm$3 months) and municipality of residence. This study will allow us to quantify relative risks and attributable fractions in a population that maintains several characteristics of low-risk developing countries but where incidence rates are as high as in Southern Europe.

A.2   Descriptive study of factors associated with a positive family history of breast or ovarian cancer. Three thousand women (2% of the intervention cohort) reported a positive history of breast or ovarian cancer. They will be compared with a suitable sample of family-negatives to assess whether they differ in any of the risk factors for BC investigated.

A.3   Descriptive study of determinants of migration outside the urban area. We tried to contact 3000 women at their original address 2 years apart. Almost half of them had moved out. We will evaluate whether their socio-demographic characteristics, as assessed by our questionnaire, would allow us to identify a stable subpopulation suitable for long-term follow-up.

B.   Descriptive studies addressing quality of care and management of breast cancer in the urban area of Manila:

B.1   Trends in the frequency of advanced disease. In 1995, before the intervention, over 75% of the breast cancers diagnosed in this population were stage III or worse. We will assess whether any significant improvement occurred by 1999.

B.2   Current and past patterns of treatment by stage, age and socio-economical level. We shall also assess the proportion of cases that receive optimal treatment according to local and external guidelines, and whether there is evidence of improvements over time.

B.3   <u>Validity of BCE performed by the nurses in the intervention compared with doctors and clinical follow-up.</u> The nurses recorded the physical characteristics of the lumps that they diagnosed as they felt them. These will be compared with the same characteristics as reported by follow-up doctors.

<u>Additional data collection and new studies.</u>

We identified two research areas that deserve more research in light of the results of the intervention. The first priority is to clarify the motives of the low compliance with referral. We need to evaluate alternative modalities to approach women that can improve their compliance with clinical follow-up if positive. The second priority concerns the quality of care and treatment to which the large majority of cases in Manila have access.

In addition to the previous points, there remains to explain the reasons of the high risk of BC in Filipino women among all Asian females. We are investigating the feasibility of cross-sectional studies on the prevalence of risk factors for breast cancer that were not covered by the questionnaire used in the intervention. We are particularly interested in markers of insulin and glucose control. These will be related to their reproductive history, body mass index and other risk factors for the disease. The objective of these studies is to establish if the prevalence of known risk factors in this population can justify the relatively high incidence to an extent consistent with what is known for Western populations.

We are exploring the feasibility of a pilot study to assess the rate of participation of the female population to a study that requires the donation of a blood sample.

CONCLUSION

Most breast cancer cases in the Philippines present at advanced stages and have a rapid unfavorable outcome. BCE undertaken by health workers appears to be an attractive compromise with a good cost-effectiveness ratio suitable for a country with limited resources. However, the sensitivity of the screening program in the real context is very low. Moreover, despite high compliance with the examination, this intervention failed to improve compliance with clinical investigation.

Several aspects related to the risk, management and care, of BC cases deserve further study.

KEY RESEARCH ACCOMPLISHMENTS

- Impact of the intervention by BSE on mortality from breast cancer.
- Risk of breast cancer in relation to several characteristics of women's reproductive life, obesity, height, alcohol consumption, family history of breast cancer and tobacco smoking.
- Prevalence of risk factors for breast cancer in the female population of Metro Manila.
- The same factors above plus education and socio-economical level as determinants of stage at diagnosis of breast cancer and survival, taking account of treatment received.
- Determinants of compliance with early diagnosis and treatment in a developing country.

REPORTABLE OUTCOMES

- Poster presentation at the Era of Hope Conference, Washington D.C., 1-4 October 1997.
- Poster presentation at the Era of Hope Conference, Atlanta, 8-11 June 2000.
- Poster presentation at the second Era of Hope Conference, Orlando, 25-28 September 2002
- REC-LINK software program – for automatic matching of records based on personal id-items (e.g. name, surname, age, date of birth, address).
- Data base of the female population resident in Metro Manila in years 1995-1996.
- Data base of new cancer cases diagnosed in the resident population 1990-2001.
- Data base of incident breast cancer cases, years 1995-2001, with clinical details of stage at diagnosis and initial treatment.

Table 1.
Results of the single round of screening, and clinical outcome after 2 years of follow-up.

Number of women interviewed:	151,168	
Number of women examined:	138,392	(91.5%)
Number positive on screening:	3,483	(2.4%)

Women CBE-positive		Cancers diagnosed by screening	Cases after 2 years of follow-up
1,220	Completed diagnostic follow-up	34	38
556	at project clinics	21	
73	at another clinic	1	
590	at project clinic after home visit	12	
1,478	Refused or follow-up incomplete		9
785	not traced		10
3,483	Total		57

Cancer detection rate per 1,000 examinations:

Total cancers found in women screen-positive:
57/138,392 = 0.41/1,000

Cancers actually detected by the screening programme:
34/138,392 = 0.25/1,000

Table 2.
Comparison of characteristics of interviewed women who refused examination, those who accepted and a sample of women living in control areas.

	compliers N=138,392	refusers N=12,776	control sample N=999
age in years (mean±SD)	44.8 ± 8.2	44.7 ± 8.4	44.0 ± 8.1
attended college/university (%)	12.3	17.7	18.6
monthly income (pesos) mean±SD	5744 ± 5590	10806 ± 12023	2786 ± 2908
median	4500	7000	1000
Income/No. of cohabitants (pesos)	1556 ± 1713	2748 ± 3292	511 ± 608
mean age at menarche	13.6 ± 1.7	13.4 ± 1.5	13.0 ± 1.4
mean age at first fullterm pregnancy	23.0 ± 4.5	24.1 ± 4.5	22.6 ± 3.8
ever used oral contraceptives (%)	13.3	8.9	6.0
ever used any contraceptive method	20.8	13.1	9.4
nulliparous (%)	10.3	16.6	2.7
women with 5 or more children (%)	32.6	25.3	21.5
never had a PAP smear (%)	69.9	72.3	73.3
smokers (%)	7.7	6.5	5.1
drinkers (%)	7.8	11.2	26.2

Table 3.
Percent rate of positive women by selected personal characteristics.

		No. positive	No. examined	positivity rate %
		3,483	138,392	
age	< 40	1,356	46,896	2.9
	40-49	1,443	53,459	2.7
	50-59	538	28,470	1.9
	60+	145	9,543	1.5
	unknown	1	24	4.2
education	max prim	925	59,803	1.5
	max secon	997	50,221	2.0
	college+	312	17,072	1.8
	unknown	1,249	11,296	11.1
pap-test	ever	1,290	39,285	3.3
	never	2,017	96,789	2.1
	don't know	176	2,318	7.6
Full-term pregnancies	<3	1,302	39,777	3.3
	3+	1,920	87,562	2.2
	missing	261	11,053	2.4
Monthly income per No. of cohabitants	low	1,679	60,799	2.8
	high	1,031	57,998	1.8
	unknown	674	19,595	3.4

Table 4.
Breast cancer cases (BC) identified in the intervention cohort after 2 years of follow-up, by screening outcome and time since PE.

	Number of women	No. incident BC in first 12 months	No. incident BC in more than 12 months	No. incident BC all	No. of cases per 1000 examined
Screen-negatives, all	*134,909*	*36*	*44*	*80*	*0.6*
Screen-positives, all	*3,483*	*41*	*16*	*57*	*16.4*
Screen-positives by screening outcome:					
Refusers and lost	2,263	11	8	19	8.4
Compliers:	1,220	30	8	38	27.9
Malignant breast cancer	34	30	4	34	
No mass or benign breast disease	1,186	-	4	4	3.4

Table 5.
Breast cancer cases that occurred among screened women, by stage at diagnosis and screening outcome. Numbers, percentages and 95% c.l.

		unknown	Localised	Regional	Distant	Total known stage
Screen-detected	No (%)	14 (42.4)	2 (10.5)	17 (89.5)	0 (0%)	19
	95% c.l.	25.5 – 60.8	1.3 – 33.1	66.9 – 98.7	0 – 17.6*	
Screen-negative or Screen-positive lost to follow-up or screen-positive benign disease		18 (17.3%)	17 (19.8%)	52 (60.5%)	17 (19.8%)	86
	95% c.l.	10.6 – 26.0	12.0 – 29.8	49.3 – 70.8	12.0 – 29.8	
Total		32 (23.4%)	19 (18.1%)	69 (65.7%)	17 (16.2%)	105
	95% c.l.	16.6 – 31.3	11.3 – 26.8	55.8 – 74.7	9.7 – 24.7	

* one-sided 97.5% c.l.

Figure 1.
Municipalities of Metro Manila and Rizal Province included in the study and covered by two population-based cancer registries.

■ 12 municipalities composing study area

▨ 4 cities of central Manila (Manila-PCS registry)
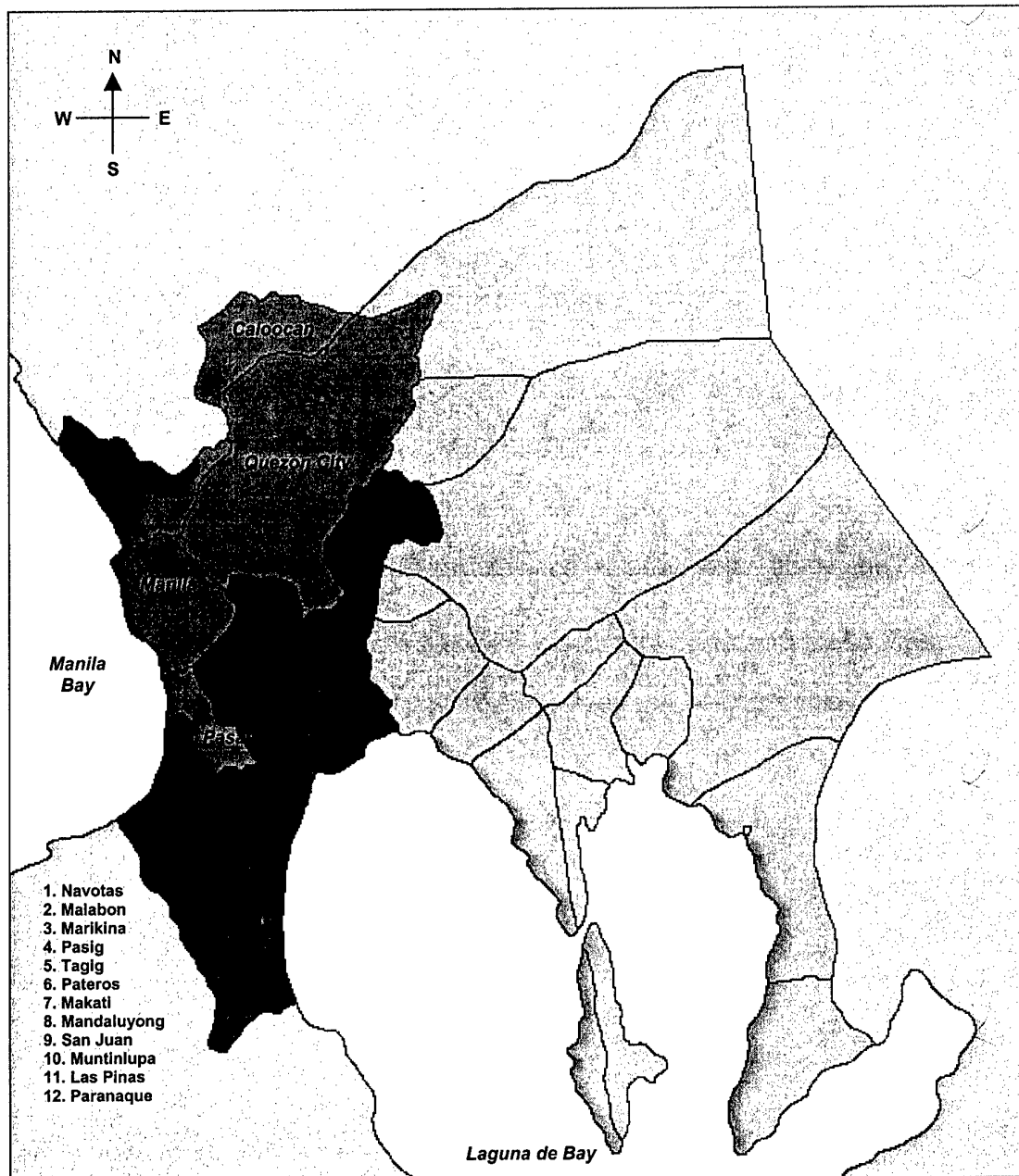
▨ 14 cities of central Province (Rizal-DOH registry)

Figure 2. Follow-up to 1999 – New cases of breast cancer identified in control (218) and intervention (211) arms as defined by electoral rolls. Of the new cases in the interviewed cohort (137), 48 were also linked with records in the electoral rolls. In brackets number screen-detected cases. In parentheses italics cohort size.
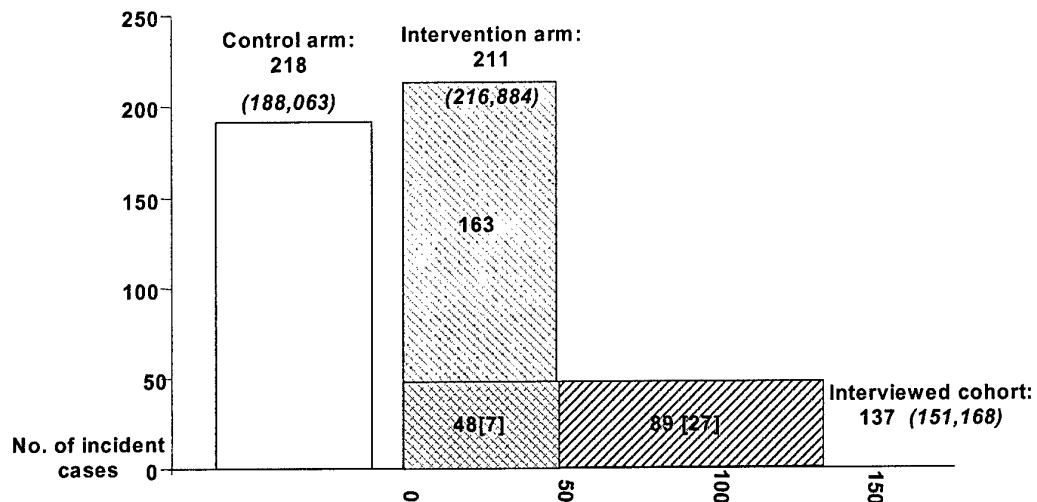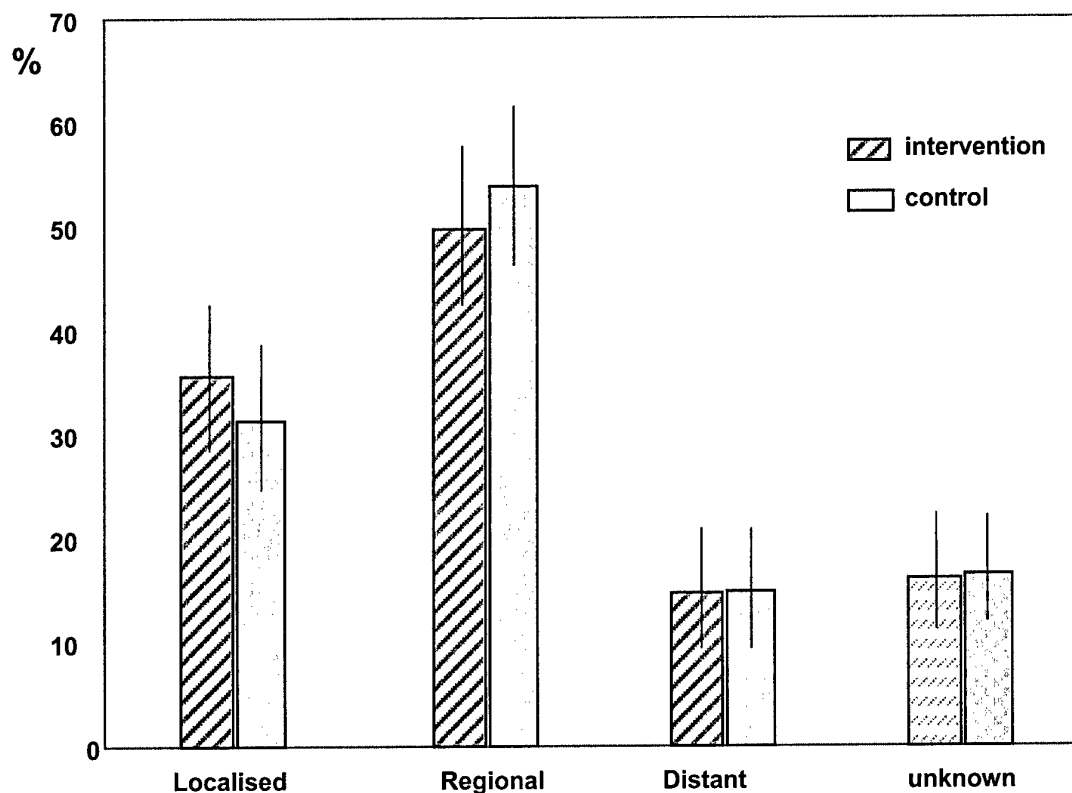

Figure 3. Incident cases by stage in the two arms defined by electoral rolls.
Percent and 95% c.l. of 211 and 218 cases in intervention and control arm respectively.

REFERENCES

1) Parkin DM, Bray FI and Devesa SS. Cancer burden in the year 2000. The global picture. Eur J Cancer 2001;37 Suppl 8:S4-66.

2) EBCTCG-Early Breast Cancer Trialists' Collaborative Group. Tamoxifen for early breast cancer: an overview of the randomised trials. Lancet 1998a;351(9114):1451-67.

3) EBCTCG-Early Breast Cancer Trialists' Collaborative Group. Polychemotherapy for early breast cancer: an overview of the randomised trials. Lancet 1998b;352(9132):930-42.

4) Peto R. Mortality from breast cancer in UK has decreased suddenly. B M J 1998;317:476-7.

5) Beral V, Hermon C, Reeves G and Peto R. Sudden fall in breast cancer death rates in England and Wales. Lancet 1995;345(8965):1642-3.

6) Nab HW, Hop WCJ, Crommelin MA, Kluck HM, van der Heijden LH and Coebergh JWW. Changes in long term prognosis for breast cancer in a Dutch cancer registry. Br Med J 1994;309:83-86.

7) Olivotto IA, Bajdik CD, Plenderleith IH,Coppin CM, Gelmon KA, Jackson SM, et al. Adjuvant systemic therapy and survival after breast cancer. N Engl J Med 1994;330 :805-810.

8) IARC, Lyon, France. IARC Breast Cancer Screening. Handbook of Cancer Prevention 2002; Vol.7. France:Lyons; 2002.

9) Barnum H and Greenberg R, Health Sector Priorities Review. Cancer. The World Bank. Washington, D.C., U.S.A.; 1991.

10) Brown ML and Fintor L. Cost-effectiveness of breast cancer screening: preliminary results of a systematic review of the literature. Breast Cancer Res Treat. 1993;25(2):113-8.

11) De Koning HJ. Breast cancer screening; cost-effective in practice ? Eur J Radiol. 2000;33:32-7.

12) World Health Organization. National Cancer Control Programmes, Geneva, Switzerland; 2002.

13) Thomas DB, Li W, Gao DL, Ray RM, Wang WW, Wu C, et al. Randomized Trial of Breast Self-Examination in Shanghai: Final Results. J Natl Cancer Inst 2002;94:1445-1457.

14) Thomas BD, Gao DL, Self SG, Allison CJ, Tao Y, Mahloch J, et al. Randomized trial of breast self-examination in Shanghai: methodology and preliminary results. J Natl Cancer Inst 1997;89:355-365.

15) Ota J, Horino T, Taguchi T, Ishida T, Izuo M, Ogita M, et al. Mass screening for breast cancer : comparison of the clinical stages and prognosis of breast cancer detected by mass screening and in out-patient clinics. Jpn J Cancer Res 1989;80:1028-1034.

16) Nelson NJ. The mammography consensus jury speaks out. J Natl Cancer Inst 1997;89:344-347.

17) Miller AB, Baines CJ and Wall C. Canadian National Breast Screening Study-2. 13-year results of a randomized trial in women aged 50-59 .J Natl Cancer Inst 2000;92:1490-1499.

18) Parkin DM, Whelan SL, Ferlay J, Raymond L and Young J, eds. Cancer Incidence in Five Continents, Vol. VII. IARC Scientific Publications. No. 143. IARC, Lyon, France;1997.

19) Parkin DM, Whelan SL, Ferlay J, Teppo L and Thomas DB, eds. Cancer Incidence in Five Continents, Vol. VIII. IARC Scientific Publications. No. 155. IARC, Lyon, France; 2002.

20) Mammatech Corporation, Gainsville, Florida U.S.A. <www.mammacare.com>, 2003.

21) Fletcher SW, O'Malley MS, Earp JL, Morgan TM, Lin S and Degnan D. How best to teach women breast self-examination. A randomized controlled trial. Ann Intern Med. 1990;112(10):772-9.